Longitudinal exploratory analysis of tumor-specific T-cell immunity and microbiome/calprotectin testing in patients with solid tumors

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To study the effect of immune modulating therapies, including anti-CTLA4, anti-PD-1, anti-PD-L1checkpoint inhibitors, and TIL therapy, on the composition and activation of systemic and local immunity, with an emphasis on the size and diversity of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Observational invasive

Summary

ID

NL-OMON55886

Source
ToetsingOnline

Brief title
TCIMM

Condition

- Metastases

Synonym
malignancy, solid tumor

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,PamGene,Vedanta,Vedanta (deel faeces samples);PamGene (klein deel bloedsamples)

Intervention

Keyword: immunological monitoring, solid tumors, T-cell immunity

Outcome measures

Primary outcome

See Objective of the study

Secondary outcome

Not applicable

Study description

Background summary

There is now widespread evidence that tumor-specific T-cell responses can contribute to the control of solid tumors. As an example, treatment of patients with the checkpoint inhibitors ipilimumab (an FDA-registered anti-CTLA4 antibody) or nivolumab (an FDA -registered anti-PD1 antibody) has shown a survival benefit in patients with different metastatic cancers, in particular melanoma, lung cancer, renal cancer and colorectal cancer. Likewise, treatment of patients with metastatic cancer with ex-vivo expanded tumor-infiltrating lymphocytes has been shown to result in clinical responses in our and other centers.
At the same time, little is known about the presence and longitudinal development of tumor-specific T-cell immunity upon immunotherapeutic treatment. Are there biomarkers that can predict the response? Does the breadth or strength of the therapy-induced T-cell response predict clinical course? Does reactivity against certain tumor-associated antigens correlate with tumor regression or with treatment-induced autoimmune disease (e.g. vitiligo in case of melanoma). Better knowledge on the T-cell responses both in peripheral blood and at the tumor site is likely to offer leads for early monitoring of treatment response, a better understanding of the mechanisms underlying the response and for the rational development of more targeted immunotherapies. Furthermore, it has been postulated that also other therapeutic strategies that have been developed or are currently in development, may exert their effect in part through stimulation of the immune system. For example, the release of melanoma-associated antigens upon inhibition of BRAF may promote the induction

of T-cell responses against these antigens. At present, not enough data are available on the relationship between treatment of solid tumors with these types of drugs and the development of tumor-specific T-cell responses, either in peripheral blood or at the tumor site. In addition, we will do multiplex kinase activity profiling for investigation of prediction of responses in collaboration with PamGene®.
Preliminary reports have suggested the microbiome in faeces may have an impact on response of melanoma patients to immunotherapy. However, the sample size of these studies is small. We want to investigate the use of shotgun metagenomic sequencing to study microbial compositions on a longitudinal basis in a larger patient cohort undergoing immunotherapy. We will, in conjunction with Vedanta®, isolate individual bacterial strains from faecal samples, pinpoint their identities by genetic analysis and determine their biological properties. It has already been shown that commensal organisms can stimulate CD8 T cells in vivo. An immediate objective of analysis of the faecal samples is determination of whether these T cell stimulatory strains are similar to strains associated with benefit in patients. Furthermore, the composition of the gut microbiome of cancer patients can be used to predict which subjects are likely to develop colitis. This will also be investigated by calprotectin testing, which is already used in inflammatory bowel patents to predict the occurrence of colitis.

Previous studies have shown that the immune system changes when patients age. For example, the numbers of dendritic cells and CD4+ naive T cells decline while the pool of terminally-differentiated CD8+ T-cells increases. In addition, the number of circulating and intratumoral myeloid derived suppressor cells (MDSC*s) increase. Hence, T-cell function may decrease and lead to impaired responsiveness to therapies aiming to boost tumor immunity. It is known that these factors are associated with clinical frailty as identified with geriatric tests that are performed in a geriatric assessment. However, no previous studies have investigated the relation between immunological ageing (so-called immunosenescence), biological ageing and immunotherapy efficacy and toxicity.

Study objective

To study the effect of immune modulating therapies, including anti-CTLA4, anti-PD-1, anti-PD-L1checkpoint inhibitors, and TIL therapy, on the composition and activation of systemic and local immunity, with an emphasis on the size and diversity of tumor-specific T-cell populations, in serial blood and tumor samples, measured by several complimentary immune analyses.

To study additional immune related parameters such as CRP, LDH, human leukocyte antigen (HLA) typing, autoantibodies, plasma cytokine levels and other factors in serum/ plasma.

To examine the impact of baseline immune parameters on treatment outcome and toxicity.

To examine faecal and mucosal samples for analysis of the microbiome together with calprotectin, serum and peripheral immune cells for predicton of toxicity (including calprotectin testing for prediction of colitis) and response.

To study the effects of immunotherapy-associated adverse events on quality of life.

To study the relation between geriatric parameters and immunosenescence in a subcohort of patients aged 65 years and older

To study the effect of immune modulating therapies on the composition of the B cell receptor repertoire in peripheral blood

Study design

All patients with solid tumors who start treatment with therapies that based on literature are expected to stimulate the immune system can be enrolled in this study.

All patients will be informed about this study consisting of two parts: I. To allow peripheral blood sampling for longitudinal analysis of tumor-reactive immune responses, and II. To allow tissue collection through serial tumor biopsies. Patients will be asked to sign an informed consent (ICF) for each part of the study with a separate signature form. After having signed the ICF, peripheral blood samples will be drawn prior to, during and after the treatment and at progression and isolated peripheral blood mononuclear cells (PBMCs) will be cryopreserved immediately for research purposes. If metastases are easily accessible and the patient signed the ICF for tumor biopsies, a biopsy will be taken before treatment, during and after therapy and at progression.

Sampling of blood and tumor tissue before, during and after therapy will be partly dependent on the type of treatment. The blood sampling of patients on immune stimulating therapy will be done before baseline (20 ml), at baseline (100 ml), at 1, and 3 months after initiation of treatment (60 ml per time point), thereafter 3 monthly (60 ml) and before switching to another immune stimulating therapy (60 ml; coinciding with response evaluation). The tumor samples of patients will be collected at start, at 3 months, at the time of signs of regression and at progression before switching to another therapy.

Faecal samples will be collected at baseline, after 6, 12 and 24 weeks for microbiome analysis. For calprotectin testing, faecal samples will be collected at baseline and after 3, 6, 9 and 12 weeks. Part of these samples will be send to Vedanta®.

The idea behind these time points for follow-up samplings is based on the mode of action of the drug and the knowledge or expectation of the time to response. For instance immunotherapy conducted with ipilimumab results in a rather slow

clinical response and therefore longer follow-up time is warranted.

In all patients aged 65 years and older, we will additionally perform a short geriatric assessment (10-15 minutes). This will take place in addition to an appointment that is already scheduled, in order to keep the burden for patients as low as possible. International guidelines advice to perform a geriatric assessment in all older patients with cancer, so this will likely become standard of care for all older patients in the near future.
During follow-up, patients will receive short follow-up consults via telephone after 6 months, 1 year and 2 years.

In patients with colitis > grade 1, we will perform extra biopsies during standard endoscopy and 2 extra questionnaires. Also 2 extra bloodsamples and feacal samples will be collected.

Study burden and risks

No toxicity is expected from drawing blood samples. However, patients may have discomfort due to taking biopsies or excisions. Biopsies will be taken from metastases that are easily accessible (mainly subcutaneous and lymph node metastases) and will in general be performed by means of ultrasonic guidance by an experienced radiologist or during endoscopy by an experienced gastroenterologist (only in case of regular endoscopies for colitis); excisions will be performed by an experienced surgeon. No toxicity is expected from faecal sample collection.

In a subgroup of patients aged 65 years and older, we will perform a short geriatric assessment (10-15 minutes). This will take place in addition to an appointment that is already scheduled, in order to keep the burden for patients as low as possible. International guidelines advice to perform a geriatric assessment in all older patients with cancer, so this will likely become standard of care for all older patients in the near future.
During follow-up, patients will receive short follow-up consults via telephone after 6 months, 1 year and 2 years.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Histologically or cytologically proven solid tumor
• Age > or = 18 years
• Performance score: WHO 0-2 at the time of study entry

Exclusion criteria

Severe anemia (Hb < 6.0 mmol/L)
Human immunodeficiency virus (HIV), chronic hepatitis B or C infection

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-07-2018
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO

Date:	15-03-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	21-09-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-01-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL59959.058.17